REROUTING ACETYL-COA AND NADPH TO IMPROVE LIPID AND OLEOCHEMICAL PRODUCTION IN YARROWIA LIPOLYTICA

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Global demand for lipid fuels and concerns about climate change have stimulated increasing efforts to produce carbon-neutral fuels directly from renewable resources. Microbially derived fatty acid fuels, the petroleum-replica fuels, have emerged as promising alternatives to meet this challenge. This is because fatty acid-based fuels offer several advantages such as high energy density, low hygroscopicity, miscibility with diesel fuels and compatibility with existing infrastructure. Recent development of the oleaginous yeast biorefinery platform has advanced the possibility to upgrade low value carbohydrates to high value fuels and oleochemicals. It is generally believed nitrogen starvation triggers lipid accumulation in oleaginous species. Under nitrogen starvation conditions, TCA metabolic activity is repressed and the overflown acetyl-CoA flux is rerouted to the fatty acid biosynthetic pathway. The central theme on this mechanism is about the acetyl-CoA supply mode: regulation of mitochondrial isocitrate dehydrogenase (ICDH). An ignored part about fatty acid biosynthesis in oleaginous yeast is the supply of NADPH, which provides the reducing equivalent to extend the carbon backbone. To overcome these challenges, we have engineered alternative cytosolic acetyl-CoA pathways to bypass the ICDH regulation, and recycled mitochondrial electrons to push the limit of lipid production in Yarrowia lipolytica. We have also been able to draw additional reducing equivalents from nitrogen metabolism and start drawing a clear picture how nitrogen starvation regulates lipogenesis in Y. lipolytica. Taken together, the reported strategy represents viable strategies to upgrade low value carbons to high value fuels and oleochemicals.